The patient-reported outcome content of international ovarian cancer randomised controlled trial protocols

Calvert, Melanie; Kyte, Derek; Mercieca-bebber, Rebecca; King, Madeleine T.

DOI:
10.1007/s11136-016-1339-x

Document Version
Peer reviewed version

Citation for published version (Harvard):
Calvert, M, Kyte, D, Mercieca-bebber, R & King, MT 2016, 'The patient-reported outcome content of international ovarian cancer randomised controlled trial protocols', *Quality of Life Research*, vol. 25, no. 10, pp. 2457–2465. https://doi.org/10.1007/s11136-016-1339-x

Article Title:

The patient-reported outcome content of international ovarian cancer randomised controlled trial protocols

Authors:

Rebecca Mercieca-Bebber[1,2], Michael Friedlander[3,4], Peey-Sei Kok[3,4], Melanie Calvert[5], Derek Kyte[5], Martin Stockler[3], Madeleine T. King[1,2,4]

Affiliations:

[1] Central Clinical School, Sydney Medical School, University of Sydney, NSW 2006, Australia.

[2] Psycho-oncology Co-operative Research Group, School of Psychology, University of Sydney. Level 6 North, Chris O'Brien Lifehouse C39Z, University of Sydney, NSW 2006, Australia.

[3] NHMRC Clinical Trials Centre, University of Sydney, NSW 2006.

[4] Australian New Zealand Gynecological Oncology Group (ANZGOG), Camperdown, NSW 2050.

[5]Institute of Applied Health Research, University of Birmingham, Birmingham, United Kingdom.

Corresponding author:

Rebecca Mercieca-Bebber

Quality of Life Office
Level 6 North, Lifehouse (C39Z)
University of Sydney, NSW 2006
Australia

Email: Rebecca.mercieca@sydney.edu.au

Phone: +612 9114 1365

Fax: +612 9036 5292

Key words:

Quality of life, patient-reported outcomes, protocol checklist, ovarian cancer, clinical trials as topic, guideline adherence

The patient-reported outcome content of international ovarian cancer randomised controlled trial protocols

Abstract:

Purpose

Patient-reported outcomes (PROs) provide the patient's perspective of the impact of treatment. Evidence suggests that PRO content of randomised controlled trials (RCT) protocols is generally suboptimal. This study aimed to describe and evaluate the PRO-specific content of ovarian cancer RCT protocols.

Methods

Published, phase III, ovarian cancer RCTs with PRO endpoints were identified following a systematic search of Medline and Cochrane databases (Jan 2000-Feb 2016). Corresponding RCT protocols were downloaded (if published) or obtained by contacting authors. Two investigators independently assessed adherence of PRO-specific content of included protocols to a checklist of 58 recommended PRO protocol items currently being developed by the International Society for Quality of Life Research (ISOQOL). Discrepancies were resolved with a third investigator.

Results

Of 41 eligible trials identified, 26 protocols were assessed (developed 1995-2010). We were unable to obtain the remaining 15 protocols. Protocols addressed a mean of 28% PRO checklist items (range 8-66%). Fifteen (58% of assessed protocols) provided a rationale for PRO assessment, 8 (31%) described a PRO objective, 24 (92%) included a PRO assessment schedule, but only 6 (23%) justified timing of PRO assessments. Twelve protocols (46%) provided staff data collection instructions, 4 (15%) included plans for monitoring PRO compliance and 16 (62%) included a PRO analysis plan.

Conclusions

On average, protocols addressed less than one-third of PRO protocol checklist items. In some cases, key guidance regarding PRO administration was lacking, which may lead to inconsistent and sub-optimal PRO methodology. Efforts are needed to improve PRO protocol content in cancer trials.

The patient-reported outcome content of international ovarian cancer randomised controlled trial protocols.

Quality of life (QOL) and other patient-reported outcomes (PROs) are important endpoints in ovarian cancer randomised controlled trials (RCTs), as the disease and its treatment can result in significant morbidities [1]. PROs are particularly important in patients with recurrent ovarian cancer where survival time is relatively short [1]. The average five-year survival rate for ovarian cancer is approximately 44-46% and there has been very little improvement in survival over the past 30 years [2,3]. PRO data are therefore crucial in evaluating the effectiveness or superiority of a therapeutic intervention, determining whether the treatment improves cancer-related symptoms or has acceptable toxicity as assessed by patients[4]. Accordingly, PROs have been included as secondary endpoints in ovarian cancer RCTs for many years [5]. However, the methodological quality of these PRO studies has, to our knowledge, never been scrutinised.

A comprehensive, high-quality protocol is critical in ensuring rigorous methodology for all RCT endpoints, including PROs [6,7]. The protocol is a key document for communicating the research rationale, standardised methodology, and ethical considerations to trial investigators and data collection staff [6]. For this reason, the quality of trial protocols is closely scrutinised by trial sponsors, ethics committees and increasingly by the broader research community when made accessible through publication or trial registration [8]. Given that RCTs are unlikely to be replicated, it is crucial that PRO studies are carefully planned, and that these plans are clearly and comprehensively described in the protocol, to yield meaningful and high-quality PRO research evidence [7].

It is of concern, therefore, that a recent review of PRO content of trial protocols in the United Kingdom found that on average, only a third of recommended PRO protocol content was addressed [9]. The study sample included RCTs from a range of health disciplines, but only four from oncology. The main objective of the present study was to describe and evaluate the PRO-specific content of ovarian cancer RCT protocols against a checklist of recommended protocol items for PRO endpoints in RCTs.

Methods

Identification of RCTs

Published, phase III, ovarian cancer RCTs of biomedical interventions with PRO endpoints were identified using three methods: 1) a systematic search of Medline and Cochrane Clinical Trials databases from 1 January 2000 - 1 February 2016 for relevant publications (see Appendix 1 for the full search strategy, which was developed with assistance from a librarian); 2) searching reference lists of included papers for additional, relevant RCTs; and 3) contacting the Gynaecologic Cancer Inter-Group (GCIG) Symptom Benefit Working Group (SBWG) to identify any additional published RCTs.

In order to maintain a focus on high-quality biomedical ovarian cancer RCTs for which PRO evidence may impact clinical practice, we excluded RCTs of mixed cancer samples (i.e. ovarian + other cancer types), samples of <50 patients, and complementary, alternative and psychological interventions. We also excluded non-English publications to avoid potential translation bias. We restricted to published RCTs, rather than searching trial registries for eligible trials, as these protocols will be included in a separate subsequent analysis involving both the publication and protocol of each RCT.

RCT protocols were downloaded from the journal's website when published as an appendix to the RCT manuscript or obtained by contacting (by email) corresponding authors of the RCT publications. Failure to respond to two emails, sent up to six months apart, was considered non-response. We were able to identify alternative email addresses for some corresponding authors via clinical networks after the contact email noted on the RCT publication had bounced. RCT authors were assured that protocols would be de-identified in analyses and publications to encourage participation, and for the benefit of education and quality improvement of future protocols. This was intended to minimise risk of original protocols being "improved" for evaluation. RCT authors were not provided with a copy of the PRO protocol checklist used for the same reason.

Protocol evaluation

Two authors (RMB, PK) independently reviewed the PRO-specific content of protocols against a checklist of recommended PRO protocol items (Appendix 2). The draft checklist content was derived from a previous systematic review [10] and is currently being refined by the International Society for Quality of Life Research (ISOQOL) Taskforce for Best Practices for PROs. Ultimately the ISOQOL Taskforce aims to develop a PRO-specific extension to the SPIRIT 2013 Statement (Standardised Protocol Items for Randomised Trials) [6,11,7]. The PRO protocol checklist includes 58 items: 56 relating to PRO-specific content of the main protocol (e.g. rationale for including PROs, assessment time points, PRO measures, planned analyses, etc.); and two general items (identification of PRO sections of the protocol in table of contents and provision of references for key PRO statements). Item P17 of the checklist (sample size for the PRO study) is directed only to RCTs with a primary PRO endpoint, however we assessed all protocols for this item regardless of PRO endpoint status, as we noticed early on (and wanted to document) that many of the protocols with secondary PRO endpoints had addressed PRO sample size.

The checklist also includes six items related to the PRO-specific content of protocol appendices. For each included protocol, a score of 1 was allocated to each PRO checklist item completely addressed, 0.5 to items partially addressed, 0 to items not addressed, and 'not applicable' (N/A) was recorded when appropriate. A total score for the main sections of each protocol (i.e. excluding the appendices) was calculated and converted to a percentage using a denominator of 58 minus the number of 'N/A' items, if any. Protocol appendices were analysed separately, as an appendix was not evaluable for all RCTs.

Inter-rater agreement was calculated using Cohen's Kappa statistic. Scoring was compared at regular intervals to ensure consistent and accurate interpretation of checklist items. Some checklist items required discussion to clarify meaning, including Item P17 (as described above); Item P9 (we accepted statements identifying PROs as a secondary endpoint, regardless of whether or not PROs were identified as a 'key' secondary endpoint); and P45 (we interpreted 'response rates' in this context as the proportion of returned questionnaires required for valid analysis, rather than clinical

response rate or change in PRO scores). Scoring discrepancies were resolved through discussion with a senior investigator (MK, MC, or MF). We tested the null hypothesis that PRO protocol checklist scores would not improve over time by calculating Spearman correlation using a pre-specified alpha level of 0.05. We also ran a series of exploratory t-tests (post-hoc) to determine whether there were differences in mean protocol checklist score for international studies (Y/N), commercial sponsorship (Y/N) and trials group sponsorship (Y/N), using a Bonferroni adjusted alpha of p=017. All analyses were conducted using SPSS (Version 22, Armonk, NY: IBM Corp).

Results

Figure 1 summarises the RCT selection process. Of 41 eligible trials identified, 26 protocols were assessed (8 published, 18 provided by authors). The remaining 15 could not be obtained (9 non-response, four email bounces, one refusal, and for one, a report was sent to us rather than the protocol). Inter-rater agreement was excellent (κ = .87, p<0.001).

<<Insert Figure 1 about here>>

Characteristics of 26 included protocols

Characteristics of 26 included protocols are included in Table 1. Protocols were developed between 1995 and 2010. Year of development was not stated for two protocols. Eleven protocols were for international RCTs (national RCTs n=7, unclear n=4). Twenty-four had a secondary PRO endpoint and one RCT had a co-primary PRO endpoint (with progression-free survival (PFS)); the status of the PRO endpoint in one RCT was unclear. The majority of RCTs had a primary endpoint of PFS (n=16), and were of chemotherapy (n=21). The most commonly used PRO measure was the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30, n=19) and ovarian cancer module (QLQ-OV28) (n=11).

<<Insert Table 1 about here>>

PRO Protocol Checklist items not relevant and excluded

Two PRO Protocol Checklist items were not relevant to any protocols in the sample and were rated N/A: none of the protocols included a validation study for PRO measures (Item P21) or permitted proxy assessment (P26). Only five protocols administered PROs to a sub-sample, therefore the item requesting justification of sampling method (P6) was only applicable to these five protocols. The item describing order of administration of multiple PRO measures (P29) was not applicable to the 19 trials that used EORTC measures (where the administration order is standardised: QLQ-C30 then QLQ-OV28), or only one PRO measure. Twelve protocols each had three N/A items and the remaining 14 protocols had four N/A items. This reduced the highest possible PRO protocol checklist total score (i.e. denominator) to 55 or 54 respectively.

PRO-specific content of protocols

Protocols addressed a mean of 28% (SD 13.7%) applicable PRO checklist items (excluding appendices), with scores ranging from 8 – 66%. Only two protocols (developed in 2004 and 2005) addressed more than 50% of recommended items, and 50% of the 26 protocols scored between 20-40%. PRO protocol checklist total scores are summarised in Table 2. There was a trend towards total

PRO protocol checklist scores improving overtime, however it was not statistically significant: *r* =0.37, p=0.07 [95% CI -0.35, 0.68] (see Appendix 3). There were no significant differences in PRO protocol checklist score for international compared to national RCTs (*p*=0.93), commercial sponsorship (*p*=0.14) or trials group sponsorship (*p*=0.28).

<<Insert Table 2 about here>>

The PRO-specific content of included protocols, including the number of protocols addressing each checklist item in full or partially, is graphed by order of adherence frequency in Figure 2. Briefly, 15 protocols (58% of the assessed protocols) provided a rationale for assessing PROs, but only eight (31%) described a PRO objective. Twenty-four (92%) included a PRO assessment schedule, but only six (23%) justified timing and 6 provided acceptable assessment windows. Twelve protocols (46%) provided staff data collection instructions and six encouraged staff discussion with patients of the importance of PRO assessments. Only four (15%) included plans for monitoring PRO compliance. Sixteen (62%) included some form of PRO analysis plan, but only nine (35%) stated how missing data would be described and two (8%) included plans for controlling for multiplicity.

<<Insert Figure 2 about here>>

Protocol appendices

Five protocols (19%) included a sample of the patient information sheet, which addressed the PRO study, four (15%) included a standardised form for collecting reasons for missing PRO data, 16 (62%) included a copy of the PRO measure being used, and five (19%) included evidence of permission to use the measure.

Discussion

Summary of findings

This study evaluates the PRO-specific content of ovarian cancer trial protocols; a patient cohort for which PROs have long been considered important endpoints in comparative effectiveness research. On average, protocols addressed less than one-third of recommended PRO checklist items. This low total score suggests that, on average, some potentially important PRO guidance is missing from protocols.

It is concerning that only 31% of protocols included a clear PRO objective, 19% included a PRO-specific hypothesis, 23% justified timing of assessment and 58% justified the PRO measure used. These are crucial to good PRO study design; they require thoughtful planning to reliably capture treatment effects and enable meaningful comparisons between treatment arms, and accordingly, need to be addressed in the protocol. If the PRO measure used is not sensitive to treatment toxicities, or if the timing of assessment is not scheduled to capture relevant toxicities, any real differences between groups or clinically important treatment effects may not be understood by the PRO assessment. Ultimately, PRO design decisions impact what treatments are approved for use and offered to patients, therefore the methodology must be carefully justified in the protocol. Regulatory bodies, such as the Food and Drug Administration (FDA) and European Medical Association (EMA) recognise the value and importance of high-quality PRO assessment in the

therapeutic approval process, and accordingly offer PRO assessment guidance [12-14]. Likewise, the Cochrane handbook offers clear guidelines for assessing the PRO evidence of intervention research in the context of conducting a systematic review [15]. We note that these guidelines (although targeted to trial publications) marry with the PRO protocol checklist used in the present study; demonstrating that trial design considerations relevant to the protocol are also relevant to publications.

Whilst the majority of protocols included basic PRO information, such as identifying the PRO as a primary or secondary endpoint (92%), specifying the assessment schedule (96%) and describing the PRO measure (85%), other key details required for standardising PRO methodology were often not addressed. For example, 54% stated whether baseline PRO assessment should occur before randomisation, only 27% provided acceptable PRO assessment time windows and 46% stated where questionnaires should be completed. PRO assessments taken a day before administration of chemotherapy are likely to differ from those taken a day or a week after chemotherapy due to differences in toxicity, and whether or not the targeted days are captured by the questionnaire's recall period [16]. Additionally, if baseline PRO assessment occurs after the intervention has commenced, the assessment may be invalid if the intervention impacts PRO scores. Some experts also recommend standardisation of assessment timing relative to the patient's appointment with their clinician, so that news of disease status does not impact PRO scores; yet only 54% of protocols addressed this. Our findings are concerning because lack of clear protocol guidance could lead to variation in PRO measurement practice, which may increase variability in the PRO data and potentially lead to bias [7,17]. Central PRO compliance monitoring is a useful strategy for identifying potential issues in real-time, to enable timely intervention and to avoid persistent problems, yet only 12% of protocols described PRO-specific monitoring procedures.

Recent evidence suggests that data collection staff often find PRO guidance inadequate [17]. Few protocols addressed staff training (8%), specified who should administer PROs (42%) or included guidance for discussing PRO assessments with patients (35%). Failure to address these points in the protocol does not necessarily imply failure to educate staff or patients within the trial, but possibly suggests that education was not standardised, and may in some cases have been insufficient[17]. A recent review of strategies to minimise avoidable missing PRO data highlighted the importance of educating staff and patients about the importance of PROs [18], thus staff and patient education about PROs is an important quality assurance concern.

Only two protocols (8%) noted PRO data would not inform patient care and no protocols included a "PRO alerts" strategy for consistent management of concerning PRO data requiring an immediate response, such as psychosocial referral for high anxiety scores[19]. Without clear guidance, staff may use their own judgment, which is likely to differ between individuals, to determine whether they examine PRO data for concerning scores, and whether and how they act on that data [20]. This may lead to co-intervention bias if their intervention impacts future PROs scores[20].

The present cohort of protocols was older (developed 1995-2010) than the protocols studied by Kyte and colleagues (2012-2013)[9], the checklists differed slightly, as did the disease focus (the present study focuses on ovarian cancer protocols; Kyte's study included trials (any disease) funded by UK National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme). Although average protocol completeness scores were similar (marginally higher in Kyte's study: 33%

compared to 28%), there were some key differences in findings between reviews. For example only 8% of the HTA protocols (compared to 58% of the ovarian cancer protocols) included a rationale for PRO assessment; 45% of the HTA cohort included PRO-specific eligibility criteria compared to only 8% of the ovarian cohort, and approximately 11% of HTA (compared to zero ovarian cancer) protocols addressed management of PRO alerts[9]. It is unclear exactly what factors contributed to differences in protocol content between the two cohorts. However, it is worth noting that the systematic review that sourced PRO protocol checklist content included a large proportion of guidance sourced from oncology [10]; possibly suggesting that PRO-specific guidance differs between medical specialisations. Alternatively, differences may reflect the changing nature of PRO assessment overtime.

We anticipated that more recent ovarian cancer RCT protocols would score higher than older protocols due to an increased need for specific details. For instance, in older trials it is likely that only paper-based PRO assessment was possible, therefore there was little need to state mode of administration in the protocol until recently, with increased use of electronic PRO assessment. Technological advances have enabled real time scoring of PRO data, allowing PRO data summaries to inform care in previously infeasible ways, for example by making automated PRO alerts possible. Our findings suggest that protocol completeness slightly improved with time, however the finding was not statistically significant. The trend we observed towards higher scores overtime was likely a result of the two highest-scoring protocols being developed in 2004 and 2005.

We did not see any differences in PRO protocol checklist score for type of sponsorship or whether the trial was international or national. We did not have sufficient study power to explore the impact of these variables in a multivariate model, yet there may be some interplay between these variables. Therefore this may be an interesting direction for future research with a larger sample size.

Our findings reinforce the need for clear, PRO-specific protocol guidance to standardise PRO methodology, improve PRO data quality and minimise the potential for bias. The modern push to publish trial protocols may persuade investigators to seek guidance for protocol development and planning of PRO studies. Publication also limits opportunity for post-hoc PRO analysis plans, as readers may verify pre-specified methodologies and analyses against those published in final manuscripts [21,22]. A recent review of British Medical Journal trial publications (September 2013-July 2014) found 22% of pre-specified outcomes were not reported and 8% of reported trial outcomes were not pre-specified[22]. Additionally, clear protocol guidance is likely to improve methodology and minimise rates of missing PRO data[18]. Recent estimates suggest approximately 20% of oncology RCTs that include a PRO endpoint in the protocol go on to publish PRO findings[23] thereby wasting research resources and participants' time [24]. The reasons for failing to publish PRO data may vary, however it is likely that many PRO studies go unpublished due to high rates of missing PRO data[25]. Although not all types of missing PRO data are preventable, strategies exist to minimise the impact of missing PRO data on data quality, and many of these must be planned and included in the protocol [18].

Strengths

The PRO protocol checklist used in this study was developed based on a comprehensive systematic review of PRO protocol guidance[10], and has undergone preliminary refinement by the ISOQOL Best Practices for PROs Taskforce. The final, internationally-endorsed PRO Protocol Checklist will be

a streamlined version of the one used in this study, with refinements based on expert and stakeholder consensus. Therefore a strongpoint of our study is that our results will be comparable to future studies evaluating protocol content. We calculated the percentage PRO protocol checklist score based only on applicable items for each protocol, enabling fair assessment and comparability across protocols. Two authors independently reviewed each protocol and inter-rater agreement was excellent.

Limitations

Despite our rigorous search strategy and persistent efforts contacting authors and engaging support from the GCIG, we were unable to obtain 37% of the 41 identified ovarian cancer trial protocols, as many trial authors were not responsive or contactable by email. This was expected, as the RCTs were published up to 16 years ago – a time when it was uncommon for protocols to be published. It is possible that protocol content of our cohort may not be representative of the overall standard of ovarian cancer protocols.

The protocol checklist used is very comprehensive and not all items are essential for all PRO endpoints; this should be taken into account when interpreting the results of the study. The final version of the PRO protocol checklist will clarify essential items, based on Delphi consensus of key, international stakeholders. We anticipate this checklist will be available in 2018. Lessons learned from this study have been logged and will feed into future development of the PRO protocol checklist via the ISOQOL Best Practices for PROs Taskforce.

We did not assess the quality of protocol content or suitability of chosen methodology to study aims; rather we used an objective approach and assessed whether checklist items were addressed partially or fully in protocols. We also did not collect information about whether other forms of guidance to complement the protocol, for example study coordinators' manuals or statistical analysis plans, were used. It is possible that other forms of guidance were used and these may have described some aspects of the PRO methodology in more detail, beyond the description provided in protocols.

Conclusions and next steps

PRO sections of ovarian cancer RCT protocols varied in comprehensiveness; however on average less than one-third of recommended PRO protocol checklist items were addressed. In some cases, guidance regarding PRO administration was lacking, which may lead to inconsistent and sub-optimal PRO methodology, and consequently sub-optimal PRO data quality. Our review highlights the need for comprehensive and clear PRO-specific content of RCT protocols; in particular, a need to specify and justify PRO assessment time points, PRO administration procedures, approaches to minimise and handle missing PRO data; and plans for scoring and analysing PRO data. Research into impact of PRO-specific content of the studied protocols on reporting and the rates of missing PRO data is ongoing. Clear guidance for PRO-specific content of protocols is needed in order to improve the standard of PRO endpoints in ovarian cancer trials.

Acknowledgements

We are grateful to the Gynaecologic Cancer Inter-Group (GCIG) Symptom Benefit Working Group (SBWG) ImPROVeD Contributor's Group leaders Professors Michael Friedlander, Felix Hilpert and Florence Joly, and to RCT investigators for providing access to trial protocols; specifically (in alphabetical order) DK Armstrong, J Berek, N Colombo, M Bookman, M Brady, J Bryce, A du Bois, G Elser, A Harkin, S Kaye, J Ledermann, K Lindemann, B Monk, T Perren, M Piccart, S Pignata, J Pfisterer, E Pujade-Lauraine, N Reed, G Rustin, J Sehouli, P Vasey, I Vergote. We also acknowledge F Roncolado and A Long for their assistance identifying eligible trials; and the International Society for Quality of Life Research Best Practices for PROs Protocol Checklist Taskforce for their contribution to developing the PRO Protocol Checklist.

Funding

This project did not receive specific grant funding. RMB is supported by Sydney Catalyst courtesy of the Cancer Institute NSW. MK is supported by the Australian Government courtesy of Cancer Australia.

Compliance with Ethical Standards

Conflicts of interest

None to declare

Ethics

This article is an analysis of PRO-specific content of RCT protocols. It did not involve direct study of human participants and therefore human ethics approval was not required.

Informed consent

This article is an analysis of PRO-specific content of RCT protocols. It did not involve direct study of human participants and therefore informed consent was not required.

Table and Figure legends

Table 1. Characteristics of the 26 ovarian cancer RCT protocols
Table 2. Total PRO protocol checklist score of 26 ovarian cancer RCT protocols
Figure 1. Flow diagram of included RCTs
Figure 2. Adherence of ovarian cancer RCT protocols to PRO Protocol Checklist items, in order of frequency

Supplementary materials

Search strategy
PRO protocol checklist
Scatterplot of total PRO Protocol Checklist scores

References

1. King, M. T., Stockler, M. R., Butow, P., O'Connell, R., Voysey, M., Oza, A. M., et al. (2014). Development of the measure of ovarian symptoms and treatment concerns: aiming for optimal measurement of patient-reported symptom benefit with chemotherapy for symptomatic ovarian cancer. *Int J Gynecol Cancer., 24*(5), 865-873.
2. Siegel, R. L., Miller, K. D., & Jemal, A. (2016). Cancer statistics, 2016. *CA Cancer J Clin, 66*(1), 7-30, doi:10.3322/caac.21332.
3. American Cancer Society (2013). Cancer Facts & Figures 2013. In American Cancer Society (Ed.). Atlanta.

4. Friedlander, M. L., & King, M. T. (2013). Patient-reported outcomes in ovarian cancer clinical trials. *Annals of Oncology, 24*(suppl 10), x64-x68.
5. Hess, L. M., & Stehman, F. B. (2012). State of the science in ovarian cancer quality of life research: a systematic review. *International Journal of Gynecological Cancer, 22*(7), 1273-1280, doi:http://dx.doi.org/10.1097/IGC.0b013e318263f02e.
6. Chan, A. W., Tetzlaff, J. M., Gotzsche, P. C., Altman, D. G., Mann, H., Berlin, J. A., et al. (2013). SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *British Medical Journal, 8*(346).
7. Calvert, M., Kyte, D., von Hildebrand, M., King, M., & Moher, D. (2015). Putting patients at the heart of health-care research. *The Lancet, 385*(9973), 1073-1074.
8. International Committee of Medical Journal Editors (2016). Clinical Trial Registration. http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html. Accessed 6 April 2016.
9. Kyte, D., Duffy, H., Fletcher, B., Gheorghe, A., Mercieca-Bebber, R., King, M., et al. (2014). Systematic evaluation of the patient reported outcome (PRO) content of clinical trial protocols. *PLOS ONE, 9*(10), e110229.
10. Calvert, M., Kyte, D., Duffy, H., Gheorghe, A., Mercieca-Bebber, R., Ives, J., et al. (2014). Patient reported outcome (PRO) assessment in clinical trials: A systematic review of guidance for trial protocol writers *PLOS ONE, 9*(10), e110216.
11. Chan, A.-W., Tetzlaff, J. M., Altman, D. G., Laupacis, A., Gøtzsche, P. C., Krleža-Jerić, K., et al. (2013). SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials. *Annals of Internal Medicine, 158*(3), 200-207.
12. European Medicines Agency Oncology Working Party (2014). *Draft Reflection Paper on the use of patient reported outcome (PRO) measures in oncology studies*.
13. Food and Drug Administration (2009). Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims.
14. Kyte, D., Reeve, B. B., Efficace, F., Haywood, K., Mercieca-Bebber, R., King, M. T., et al. (2016). International Society for Quality of Life Research commentary on the draft European Medicines Agency reflection paper on the use of patient-reported outcome (PRO) measures in oncology studies. *Qual Life Res., 25*(2), 359-362.
15. Patrick, D. L., Guyatt, G. H., Acquadro, C., & Cochrane Patient Reported Outcomes Methods Group (2011). Chapter 17: Patient-reported outcomes. In J. Higgins, & S. Green (Eds.), *Cochrane Handbook for Systematic Reviews of Interventions* (Vol. 5.1.0.): The Cochrane Collaboration.
16. Aaronson, N. K. (1990). Quality of life research in cancer clinical trials: a need for common rules and language. *Oncology, 4*(5), 59-66.
17. Kyte, D., Ives, J., Draper, H., Keeley, T., & Calvert, M. (2013). Inconsistencies in Quality of Life Data Collection in Clinical Trials: A Potential Source of Bias? Interviews with Research Nurses and Trialists. *PLOS ONE, 8*(10), e76625, doi:10.1371/journal.pone.0076625.
18. Mercieca-Bebber, R., Palmer, M., Brundage, M., Calvert, M., Stockler, M., & King, M. Design, implementation and reporting strategies to reduce the instance and impact of missing patient-reported outcome (PRO) data: A systematic review. *BMJO,* In press. Accepted 18 May 2016.
19. Kyte, D., Draper, H., & Calvert, M. (2013). Patient-reported outcome alerts: Ethical and logistical considerations in clinical trials. *JAMA, 310*(12), 1229-1230.
20. Kyte, D., Ives, J., Draper, H., & Calvert, M. (2016). Management of Patient-Reported Outcome (PRO) Alerts in Clinical Trials: A Cross Sectional Survey. *PLOS ONE, 11*(1), e0144658.
21. Skogvoll, E., & Kramer-Johansen, J. (2013). Publication of clinical trial protocols – what can we learn? *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine, 21*, 12-12.
22. Weston, J., Dwan, K., Altman, D., Clarke, M., Gamble, C., Groves, T., et al. (2015). Selective reporting in clinical trials - an examination of discrepancy rates in pre-specified and reported

outcomes in articles submitted to the BMJ. *Trials, 16*(2), 1-1, doi:10.1186/1745-6215-16-s2-o72.
23. Schandelmaier, S., Conen, K., von Elm, E., You, J. J., Blumle, A., Tomonaga, Y., et al. (2015). Planning and reporting of quality-of-life outcomes in cancer trials. *Ann Oncol., 26*(9), 1966-1973.
24. Glasziou, P., Altman, D. G., Bossuyt, P., Boutron, I., Clarke, M., Julious, S., et al. (2014). Reducing waste from incomplete or unusable reports of biomedical research. *The Lancet, 383*(9913), 267-276.
25. Friedlander, M., Mercieca-Bebber, R., & King, M. (2016). Patient Reported Outcomes in Ovarian Cancer Clinical Trials - Lost Opportunities and Lessons Learned. *Annals of Oncology, 27*(S1), i66-71.

Table 1. Characteristics of the 26 ovarian cancer RCT protocols[1]

Characteristic		**No. of protocols (%)**
Year of development	1995 – 2000	10 (38)
	2001 - 2005	10 (38)
	2006 - 2010	4 (15)
	Unclear from protocol	2 (8)
Recruitment	International recruitment (i.e. >1 country)	11 (42)
	National recruitment	7 (27)
	Unclear if international recruitment	8 (31)
Intervention	Chemotherapy	21 (81)
	Targeted therapy	5 (19)
	Surgery	1 (4)
Primary endpoint	Progression-free survival (PFS)	15 (58)
	Overall survival	3 (12)
	Survival (other)	3 (12)
	All-cause mortality	2 (8)
	PFS and QOL (co-primary)	1 (4)
PRO endpoint status	Co-primary	1 (4)
	Secondary	24 (92)
	Unclear from protocol	1 (4)
PRO measures used	EORTC QLQ-C30 [2]	19 (73)
	EORTC QLQ-OV28 [3]	11 (42)
	FACT-O [4]	6 (23)
	Other FACIT [5] measures	3 (12)
	EQ-5D[6]	3 (12)
	Other	3 (12)
Sponsors	Clinical Trials Group	19 (73)
	Commercial/pharmaceutical	3 (12)
	Co-sponsored: Trials group and commercial	3 (12)
	Unclear	1 (4)

[1]RCTs are not identified in this manuscript as per agreement with the RCT authors. [2] European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30); [3] ovarian cancer module (QLQ-OV28), which is used with the QLQ-C30; [4] Functional Assessment of Cancer Therapy – Ovarian Cancer Module (FACT-O); [5] Functional Assessment of Cancer Therapy (FACIT); [6] the EuroQOL-5 dimensions (EQ-5D).

Table 2. Total PRO protocol checklist score of 26 ovarian cancer RCT protocols

	n	Mean (SD) total score	Mean total score %	Total score (lowest - highest extreme)
Protocols with 54 applicable PRO checklist items	14	13.8 (7.0)	25.6	4.5 - 27
Protocols with 55 applicable PRO checklist items	12	17.4 (7.8)	31.6	7 - 36
All protocols	26	15.5 (7.5)	28.4	4.5 - 36

Figure 1. Flow Diagram of included RCTs

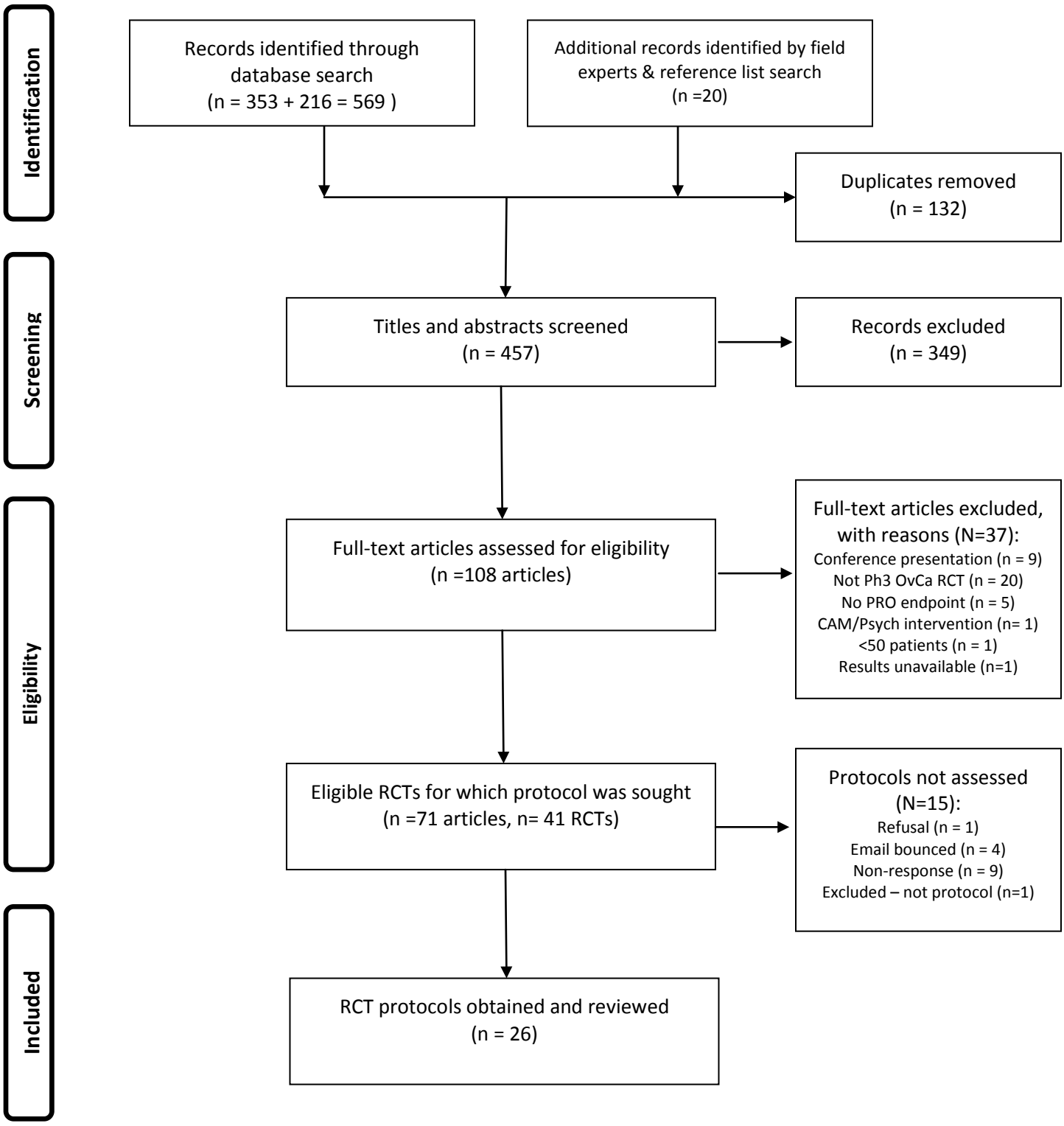
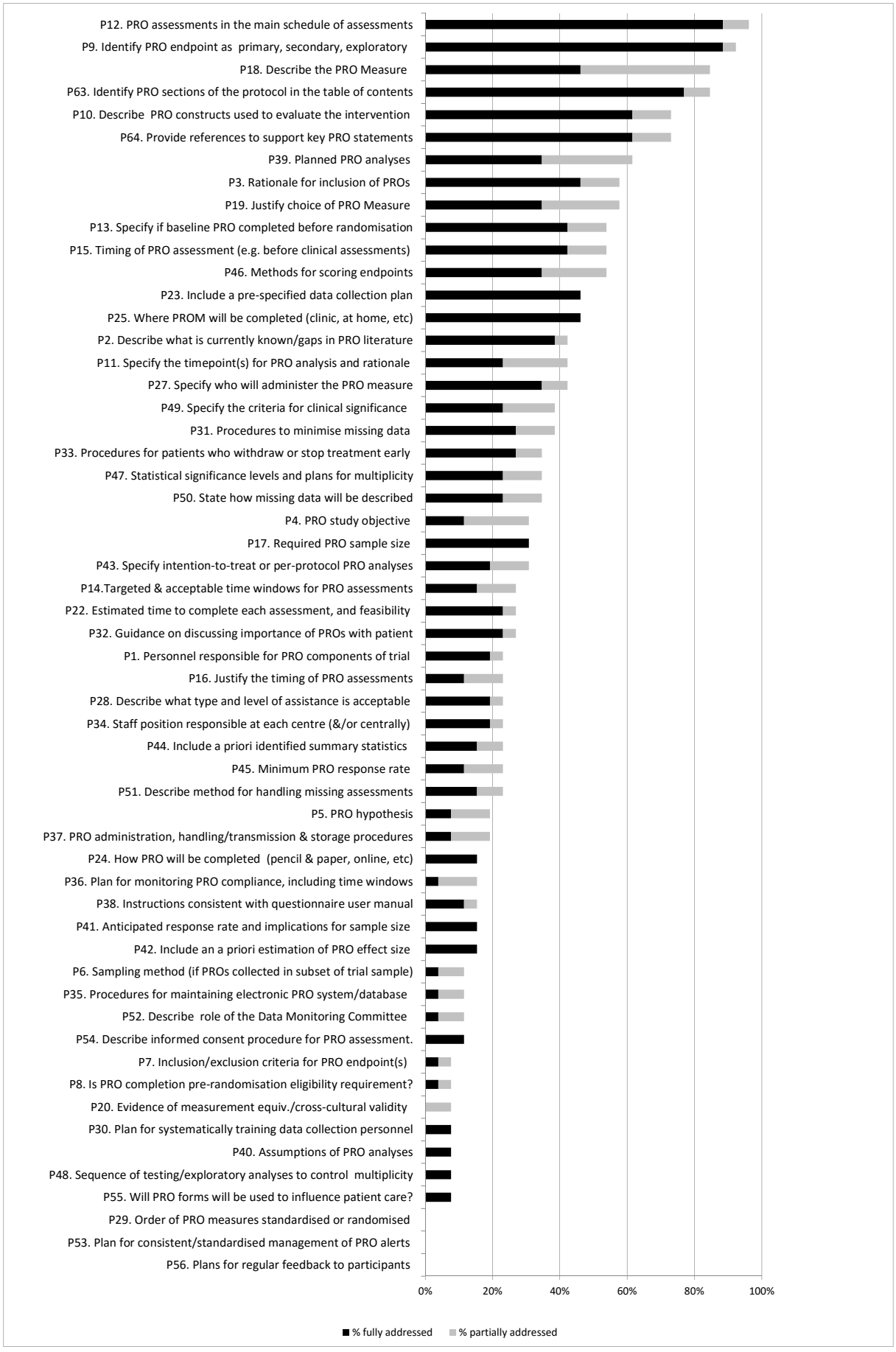


Figure 2. Adherence of 26 Phase III ovarian cancer RCT protocols to the PRO protocol checklist, in order of frequency



Appendix 1. Search strategy

Rebecca Mercieca-Bebber, Michael Friedlander, Peey-Sei Kok, Melanie Calvert, Derek Kyte, Martin Stockler, Madeleine T. King. The patient-reported outcome content of international ovarian cancer randomised controlled trial protocols.

Medline OVID 1/2/2016

	Ovarian cancer terms	
1	(ovar* adj (neoplasm$ or cancer or carcinoma or tumo$ or malignan$)).tw.	49275
2	Ovarian neoplasms.sh.	67150
	QOL/patient-reported outcome terms	
3	self-report*.tw.	87069
4	Quality of life.sh.	131753
5	Quality of life.tw.	152958
6	"health status".tw.	37664
7	'health utilit*'.tw.	1140
8	'symptom assessment'.tw.	1445
9	physical function*.tw.	13473
10	social function*.tw.	9121
11	"social wellbeing".tw.	134
12	'sexual function*'.tw.	9161
13	PRO.tw.	115062
14	PROM.tw.	1390
15	HRQOL.tw.	8025
16	HRQL.tw.	2411
17	QOL.tw.	20265
18	QL.tw.	1078
19	"functional status".tw.	17166
20	(symptom* adj (improv$ or change$ or deteriorat$ or assessment$ or burden or distress)).tw.	15265
21	Questionnaire*.tw.	308065
22	Survey.tw.	325454
	Trial terms	

23	"trial".tw.	367927
24	RCT.tw.	9071
25	randomi$ study.tw.	23300
	Groupings	
26	1 or 2	75642
27	or/3-22	936149
28	23 or 24 or 25	390904
29	26 and 27 and 28	349
30	limit 29 to (english language and yr="2000 -Current")	308
31	26 and 27	2913
32	limit 31 to (clinical study or clinical trial, phase iii or clinical trial or controlled clinical trial)	160
33	limit 32 to (english language and yr="2000 -Current")	111
34	30 and 33	66
35	**30 or 33**	**353**

Cochrane central register for controlled trials 1/2/2016

	Searches	Results
1	(ovar* adj (neoplasm$ or cancer or carcinoma or tumo$ or malignan$)).tw.	2506
2	Ovarian neoplasms.sh.	1053
3	self-report*.tw.	11240
4	Quality of life.sh.	12973
5	Quality of life.tw.	28934
6	"health status".tw.	2981
7	'health utilit*'.tw.	220
8	'symptom assessment'.tw.	286
9	physical function*.tw.	3362
10	social function*.tw.	1594
11	"social wellbeing".tw.	16
12	'sexual function*'.tw.	1336
13	PRO.tw.	3578
14	PROM.tw.	221
15	HRQOL.tw.	1572
16	HRQL.tw.	485
17	QOL.tw.	5175
18	QL.tw.	180
19	"functional status".tw.	1896
20	(symptom* adj (improv$ or change$ or deteriorat$ or assessment$ or burden or distress)).tw.	4663
21	Questionnaire*.tw.	33367
22	Survey.tw.	8356
23	1 or 2	2681
24	or/3-22	79824
25	23 and 24	278
26	**limit 25 to (english language and yr="2000 -Current")**	**216**

Appendix 2. PRO protocol checklist

Rebecca Mercieca-Bebber, Michael Friedlander, Peey-Sei Kok, Melanie Calvert, Derek Kyte, Martin Stockler, Madeleine T. King. The patient-reported outcome content of international ovarian cancer randomised controlled trial protocols.

	PRO Protocol checklist item
P1	List **personnel responsible for PRO** components of trial
P2	Describe **what is currently known about PROs** in this area and explain the gaps in literature
P3	Provide a **rationale for the inclusion of PROs** as appropriate to the study population, intervention, context, objectives and setting
P4	State the **PRO study objective** in relation to PRO domain/s, patient population and timeframe
P5	State the **PRO hypothesis** & corresponding null hypothesis and to which outcome(s) the hypothesis relates
	Methods
P6*	If PROs will be collected in a subset of the study population or in specific centres, include a description/rationale for the **sampling method**
P7	State the **inclusion/exclusion criteria for PRO** endpoint(s) (e.g., language/reading requirements)
P8	Specify if **PRO completion is pre-randomisation** eligibility requirement
P9	Identify the **PRO endpoint as the primary, secondary** (and if so - whether a key/important secondary), or an exploratory endpoint
P10	Describe the **PRO constructs** used to evaluate the intervention e.g. overall QOL, specific domain, specific symptom
P11	Specify the **timepoint(s) for PRO analysis** (including the principle timepoint of interest) and provide the rationale for these
P12	Include **PRO assessments** in the main protocol schedule of assessments, specifying which PRO measures (PROMs) will be used at each assessment
P13	Specify if **baseline PRO assessment should be completed before randomisation**
P14	Specify the targeted time and acceptable **time windows** for each PRO assessment
P15	If PROs are to be completed in the clinic: **specify timing of PROM delivery** in relation to clinical assessments (e.g. before/whilst/after seeing clinician and/or clinical assessments)
P16	**Justify the timing of PRO assessments**. Scheduled PRO assessments should link to research questions, hypotheses, length of recall, disease/treatment natural history, planned analysis and time of comparison must be comparable for both arms
P17^	If PRO is the primary endpoint, state the required PRO **sample size,** otherwise discuss the power of the PRO analysis
	PROM & administration
P18	**Describe the PROMs** including, number of items/domains, instrument scaling/scoring, reliability, content and construct validity, responsiveness, sensitivity, acceptability, recall period. Provide references as appropriate
P19	**Justify choice of PROM**(s) by linking specific domains/items to clinical justifications and hypotheses
P20	Provide **evidence of measurement equivalence across modes** (i.e., when mixing modes of PRO data collection) and/or **of cross cultural validity** where different language versions of questionnaires are used
P21*	**Outline plans for evaluation of measurement properties, if appropriate** (e.g. if not previously validated in the population of interest)
P22	Specify the **estimated time to complete each assessment**, and discuss feasibility of assessment for the population"
P23	Include a pre-specified **data collection plan**
P24	Specify **how PROM will be completed** (e.g. pencil and paper, online, etc)
P25	Specify **where PROM will be completed** (e.g. clinic, home, etc)

	PRO Protocol checklist item
P26*	Where applicable, **justify use of proxie**s (define conditions under which proxy assessment is permissible)
P27	Specify **who will administer the PROM** (e.g., a physician, nurse, etc)
P28	If it is permissible for another person to help the study participant complete the PROM, describe what type **and level of assistance is acceptable**
P29*	If more than one PROM will be used, **specify whether the order of administration will be standardised or randomised**
P30	Include a **plan for systematically training** and contacting local site personnel to ensure that they understand the content and importance of collecting PRO data. Ideally coordinated by a lead data manager who monitors PRO completion rates in real time and communicates with sites if completion rates are suboptimal
P31	Specify procedures for **data collection and management methods to minimise missing data**. E.g. checking completed PROMs (including who will check forms and how will they deal with missing PROMs or missing items).
P32	Include **guidance on discussing importance of PROs with patient**
P33	Establish process for PRO assessment at (and beyond) **withdrawal for patients who withdraw early** from a study or who go 'off-study'/'off treatment'
P34	Specify that a named person/position at each centre (and/or centrally) be nominated to take r**esponsibility for administration**, collection and checking of PROM - specify whether this is or is not the treating clinician
	Data management
P35	Specify how an e**lectronic PRO system/database will be maintained** and how investigator will meet regulatory requirements and ensure data integrity and security
P36	Specify **plan to monitor PRO compliance,** including adherence to time windows
P37	Include an **overview of PRO administration** (data collection), and d**ata handling/transmission and storage procedures**
P38	Ensure **plans for administration of PROM(s)** are consistent with each PROM's user manual
	Analyses
P39	Include an a priori description of all **planned PRO analyses** pertaining to the study hypotheses
P40	State the **assumptions of PRO analyses**
P41	State the **anticipated response rate** and implications for the sample size
P42	Include an a priori estimation of **PRO effect size**
P43	S**pecify intention-to-treat** or per-protocol PRO analyses.
P44	Include a prior**i identified summary statistics** (as appropriate)
P45	Specify the **minimum PRO response rate** and acceptable degree of timing deviation (i.e acceptable time windows for each PRO assessment timepoint) before the PRO objective is compromised
P46	Describe **methods for scoring endpoints.** Where possible, **reference scoring manuals** for summated scales from PROM (domain-specific &/or total) & **methods for handling missing items,** and methodological papers for composite endpoints (e.g. QTWiST)
P47	State **statistical significance levels** and include plans for multiplicity/controlling type 1 error
P48	**Pre-specify sequence of testing/exploratory analyses to control for multiplicit**y or pre-specify domains (e.g. in a regulatory trial/labelling claim) (Common in pharma trials. Involves pre-specifying domains that alpha would be spent on, or ordering the domains in priority & alpha would be spent down the list)
P49	Specify the **criteria for clinical significance** (e.g. state minimal [clinical] important difference and/or responder definition (size and duration of benefit))
P50	State how **missing data will be described**
P51	Describe method for **handling missing assessments** (e.g. approach to imputation and sensitivity analyses)
	Monitoring
P52	Describe the **role of the Data Monitoring Committee** and Quality Assurance for PROs
P53	Include an a priori plan for consistent/standardised **management of PRO alerts** (symptoms/issues

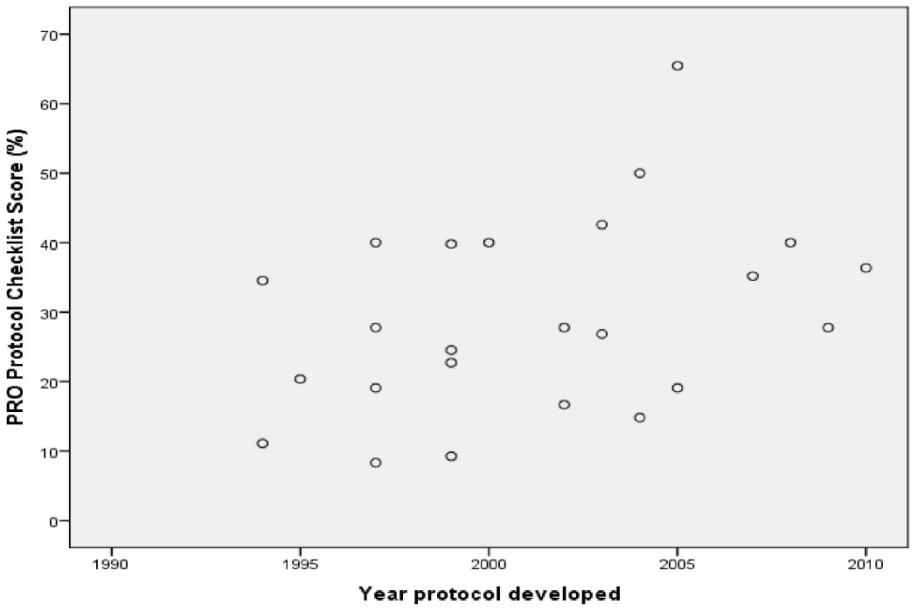
	PRO Protocol checklist item
	reported by patients that exceed a pre-defined level of severity) to be clearly communicated to all appropriate trial staff
P54	Describe i**nformed consent procedure** for PRO assessment.
P55	Specify whether **PRO forms will be used to influence therapy or patient management**
P56	Include detailed **plans for regular feedback to participants** via letter/newsletter on PRO aspect of study
	General Approach to Protocol
P63	Identify PRO sections of the protocol in the **table of contents**
P64	Provide **references** to support key PRO statements

*This item was N/A for some or all protocols

^We assessed all protocols for this item regardless of PRO endpoint status

Appendix 3. PRO protocol checklist scores over time

Rebecca Mercieca-Bebber, Michael Friedlander, Peey-Sei Kok, Melanie Calvert, Derek Kyte, Martin Stockler, Madeleine T. King. The patient-reported outcome content of international ovarian cancer randomised controlled trial protocols.



Note: year of protocol development was unclear for 2 protocols, therefore this plot includes PRO protocol checklist scores (%) for 24 ovarian cancer RCTs. There was a trend towards total PRO protocol checklist scores improving over time, however it was not statistically significant: r =0.37, p=0.07 [95% CI -0.35, 0.68].